

[Drug Name](#) | [Mechanism of Action & Pharmacokinetics](#) | [Indications & Status](#) | [Adverse Effects](#) | [Dosing](#) | [Administration Guidelines](#) | [Special Precautions](#) | [Interactions](#) | [Recommended Clinical Monitoring](#) | [References](#)

A DRUG NAME: FLUOROURACIL

SYNONYM(S): 5-Fluorouracil, 5FU

COMMON TRADE NAME(S): Adrucil® (Teva - US), Efudex® Cream (Valeant)

B MECHANISM OF ACTION AND PHARMACOKINETICS

Fluorouracil was developed in 1957 based on the observation that tumour cells utilized the base pair uracil for DNA synthesis more efficiently than did normal cells of the intestinal mucosa. It is a fluorinated pyrimidine antimetabolite that is metabolized intracellularly to its active form, fluorouridine monophosphate (FdUMP). The active form inhibits DNA synthesis by inhibiting thymidylate synthetase and the normal production of thymidine. Effects on RNA (incorporation into RNA and RNA inhibition) occur especially with bolus administration. Fluorouracil is cell cycle phase-specific (S-phase).

Absorption	Oral: 28-100% Topical: Insignificant (<5-10%)
Distribution	Into all body water by passive diffusion, crosses placenta, high and persistent levels in malignant effusions Cross blood brain barrier? Yes Vd 0.1-0.4 L/kg PPB 10%
Metabolism	Activated in target cells, 80% of dose degraded in liver by dihydropyrimidine dehydrogenase (DPD) Active metabolite(s) FdUMP, FUTP, DdUTP Inactive metabolite(s) Yes
Excretion	60-80% excreted as respiratory CO ₂ , 2-3% by biliary system. Higher clearance occurs in IV infusions than IV injections, due to saturation of metabolic or transport processes at higher drug concentrations. Urine 15-20% as intact drug within 6 hours t ½ 6-20 minutes; dose-dependent Cl 0.6-2.3 L/min, 16 mL/min/kg, women 155 L/h/m ² , men 179 L/h/m ²

C INDICATIONS AND STATUS

- | | |
|--|---|
| <ul style="list-style-type: none"> * Breast cancer (adjuvant/palliative) * Colorectal cancer (adjuvant/palliative) * Gastric cancer * Pancreatic cancer * Cancer of urinary bladder * Cancer of the prostate * Cancer of the head and neck * Cancer of the ovary * Superficial basal cell carcinoma (topical) * Premalignant keratoses (topical) * <i>Health Canada approved indication</i> | <p>Other uses include:</p> <p>Endometrial cancer
Hepatic cancer</p> |
|--|---|

[▲ Back to Top](#)**D ADVERSE EFFECTS**

ORGAN SITE	SIDE EFFECT	ONSET	
Cardiovascular	Asymptomatic ECG changes (69%), arrhythmias	I	
	Myocardial ischemia	I	
	Pericarditis, heart failure (rare)	I	
Central nervous system	Acute cerebellar syndrome (< 1%, high doses or intensive daily regimens)	E	D
	Photophobia, optic neuritis, oculomotor	E	
	Acute encephalopathy/euphoria(rare), leucoencephalopathy (rare)	E	D
Dermatologic	Alopecia (mild)	E	
	Hyperpigmentation, thrombophlebitis	E	
	Rash (extremities, sometimes on trunk)	E	
	Nail changes	E	
	Photosensitivity, dry skin	E	
	Palmar-plantar erythrodysesthesia	E	
	Radiation recall reaction (rare)	I	
	Erythema, necrosis (topical application)	I	E
Extravasation hazard (refer to Appendix 2)	Irritant		

[▲ Back to Top](#)

D	ADVERSE EFFECTS (continued)		
	ORGAN SITE	SIDE EFFECT	ONSET
Gastrointestinal	Nausea and vomiting	I	
	<u>Mucositis</u>		E
	GI ulcers and bleeding (rare)		
	Anorexia		E
	<u>Diarrhea</u>		E
Hematologic	<u>Myelosuppression (very common ± infection, bleeding)</u>		E
	Immunosuppression		E
	Hemolytic-uremic syndrome (with mitomycin), hemolytic anemia		
Hypersensitivity	Type I (anaphylactoid, rare)	I	
Injection site	Chemical phlebitis	I	
Ocular	Lacrimation; tear duct fibrosis	I	L
	Conjunctivitis	I	
Hepatic	Hepatic toxicity (rare)		D

Dose-limiting side effects are underlined.

I = immediate (onset in hours to days); E = early (days to weeks);
D = delayed (weeks to months); L = late (months to years)

Following longer IV infusions, ***mucositis, hand-foot syndrome and diarrhea*** occur most commonly. Diarrhea may be profuse and life-threatening following administration of leucovorin with fluorouracil. ***Leukopenia*** is the usual dose-limiting toxicity after IV bolus administration

Patients with dihydropyrimidine dehydrogenase deficiency are at risk of severe life-threatening toxicity with fluorouracil. While severe deficiency is rare, 3-4% of the population has some degree of DPD deficiency.

Excessive lacrimation occurs frequently. Transient blurring of vision, eye irritation and excessive ***nasal discharge*** have also been reported. The onset of eye symptoms may occur at any time during treatment. Fluorouracil has been demonstrated in tear fluid causing acute and chronic conjunctivitis that can lead to tear duct fibrosis.

D ADVERSE EFFECTS (continued)

Acute cerebellar syndrome is manifested as ataxia of the trunk or extremities, disturbance of gait and speech, coarse nystagmus and dizziness. The ataxia syndrome is related to peak plasma levels of the drug rather than to cumulative dose, and is therefore more common with bolus doses than with infusions. It usually resolves after treatment is discontinued, but may persist in some cases.

Palmar-plantar erythrodysesthesia or hand-foot syndrome has been noted with protracted and high dose continuous infusion (23-82%). The syndrome begins with dysesthesias of the palms and soles that progress to pain and tenderness. There is associated symmetrical swelling and erythema of the hand and foot. Treatment with 50 or 150 mg of pyridoxine daily has been associated with reversal of the syndrome. The syndrome resolves gradually over 5 to 7 days with cessation of drug infusion.

Cardiotoxicity has been reported and may be caused by coronary vasospasm, endothelial cell damage or increased thrombogenicity. It occurs in less than 10% of patients, of which up to 8% may be fatal. Cardiac effects include ECG changes, angina, arrhythmias, myocardial infarction, heart failure and are usually reported within 72 h of the first cycle of fluorouracil. Cardiotoxicity is independent of dose or underlying cardiac risk factors, but may be more common with infusions. Patients should be rechallenged only when there are no other treatment options.

Fluorouracil has the potential to enhance radiation injury to tissues. While often called **radiation recall reactions**, the timing of the radiation may be before, concurrent with or even after the administration of the fluorouracil. Recurrent injury to a previously radiated site may occur weeks to months following radiation.

Hemolytic-uremic syndrome has been reported when used in combination with mitomycin C.

When applied to a lesion, the following occurs: Erythema, usually followed by vesiculation, erosion, ulceration, necrosis and epithelization. The lower frequency and intensity of activity in adjacent normal skin indicates a selective cytotoxic property. An occlusive dressing is not essential, and may increase the incidence of inflammatory reactions in adjacent normal skin. Therapy is usually continued to reach the erosion, necrosis and ulceration stage (2-4 weeks), after which healing occurs over 4-8 weeks. The most frequent local reactions are pain, pruritus, hyperpigmentation and burning at the application site. Avoid prolonged exposure to sunlight or ultraviolet light during treatment as the intensity of the reaction may be increased.

[▲ Back to Top](#)

E

DOSING

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Consider a reduced starting dose for patients who are heavily pretreated, malnourished or have poor performance status, or in patients with large third space collections or edema.

IV bolus: q4w: 250-500 mg/m² day x 5 days
q4w: 500-600 mg/m² days 1 & 8

IV infusion: q3w: 200 mg/m²/day on days 1-21 as continuous infusion
q3-4w: 750-1000 mg/m²/day x 4-5 days as continuous infusion
q2w: 600 mg/m²/day x 22 hours on days 1 and 2
q2w: 2400 mg/m² x 46 hours starting on day 1

Dosage with toxicity: Modify according to protocol by which patient is being treated; if no guidelines available, refer to [Appendix 6](#) "Dosage Modification for Myelosuppression"

Toxicity or Counts (x 10 ⁹ /L)	During Cycle	For Next cycle
Platelets < 80 or AGC < 1.5	Hold*	May consider ↓
Bleeding, febrile neutropenia	Hold*	↓ by 25%
≥ grade 3 GI	Hold*	↓ by 25%
CNS	Hold*	↓ by 25%,
Cardiac	Hold*	Consider discontinuing
* Do not retreat until AGC ≥ 1.5 , platelets ≥ 100 and organ toxicity ≤ grade 2. With severe toxicity, consider testing for DPD deficiency prior to rechallenge.		

Dosage with renal impairment: No adjustment required, although reduction may be considered with severe renal insufficiency

Dosage with hepatic impairment: Omit if bilirubin > 4 x ULN (upper limit of normal). Consider dose reduction with moderate to severe hepatic impairment

Topical: Twice daily: x 1-4 weeks. Stop when erosion evident, usually 2-4 weeks. Allow 1-2 months for healing.
Total area treated at one time should not exceed 500 cm² (23x23 cm). Larger areas should be treated one section at a time.

[▲ Back to Top](#)

F

ADMINISTRATION GUIDELINES (see [Appendix 3a](#))

IV PUSH OR INTERMITTENT INFUSION:

- Slow push through sidearm of free-flowing IV (5% Dextrose, Normal Saline or 2/3-1/3)
- May be given by direct IV push, followed by a Normal Saline flush, if no IV line has been set up
- May be mixed in 50ml minibag (NS or DSW); infuse over 15 min.
- Protect from light.

IV CONTINUOUS INFUSION:

- Continuous infusion using CADD infusion pump, or similar device
- Infuse through central venous access device, if available
- Infusion volume and duration depend on protocol.
- Infuse through patent peripheral venous catheter, if infusion for only 3-5 days; Inspect peripheral infusion sites daily and replace if evidence of irritation or extravasation
- Protect from light
- Incompatible with doxorubicin, epirubicin, diazepam, methotrexate and cytarabine; line must be flushed between administrations of fluorouracil and these agents

TOPICAL:

- Apply a thin layer to the affected area.
- Glove or non-metal applicator preferred. If fingertips used, wash hands immediately afterward.
- Exercise care when applying the cream near the eyes, nostrils and mouth.

[▲ Back to Top](#)

G

SPECIAL PRECAUTIONS

Fluorouracil is **contraindicated** in patients with poor nutritional state, depressed bone marrow function (prior pelvic irradiation / marrow infiltration), or potentially serious infections and in patients with known hypersensitivity to the drug.

It should be used with extreme caution in patients who have undergone recent major surgery, or are suspected to have DPD deficiency.

Fluorouracil is **teratogenic**, **mutagenic**, and also has potential **carcinogenic** effects; it should not be used in **pregnancy**. Adequate contraception should be used by both sexes during treatment and for at least 6 months after the last dose. Animal studies suggested that male **fertility may be affected**. **Breast feeding** is not recommended due to the potential secretion into breast milk.

[▲ Back to Top](#)

H

INTERACTIONS

Laboratory tests for bilirubin (icteric index) and urinary 5-HIAA may increase or have false positive results. Increases in T3 and T4 levels have been reported in euthyroid, advanced breast cancer patients treated with single agent fluorouracil, and these changes were reversible within 4 weeks after the end of treatment.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Allopurinol	decreased toxicity of fluorouracil	possibly inhibition of thymidine phosphorylase	caution
Mitomycin	increased incidence of hemolytic-uremic syndrome	unknown	
Cimetidine	increased serum concentrations of fluorouracil	appears to interfere with fluorouracil metabolism	observe for increased toxicity of fluorouracil
Leucovorin	increased cytotoxic and toxic effects of fluorouracil	Leucovorin stabilizes the bond to thymidylate synthetase	some protocols are designed to take advantage of this effect; monitor toxicity closely
Metronidazole	enhanced toxicity of fluorouracil	decreased clearance of fluorouracil	monitor for increased toxicity of fluorouracil
Phenytoin	Increased phenytoin levels and toxicity	Possible inhibition or decreased synthesis of CYP2C9 by fluorouracil	Monitor phenytoin levels and patient
Thiazide diuretics	increased myelosuppression	decreased renal excretion of fluorouracil	consider an alternative antihypertensive
Warfarin	increased effect of warfarin	Decreased CYP2C9 enzymes for metabolism; reduced warfarin clearance	monitor INR closely; adjust warfarin doses accordingly

I RECOMMENDED CLINICAL MONITORING**Recommended Clinical Monitoring****Suggested Clinical Monitoring**

- Regular clinical assessment and grading of stomatitis, diarrhea, bleeding, infection, local site toxicity, skin effects (rash or hand-foot-syndrome). Grade toxicity using the current [NCI Common Toxicity Criteria Version](#).
- Baseline and regular CBCs
- Baseline liver & renal function tests

[▲ Back to Top](#)

J REFERENCES

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[▲ Back to Top](#)